

A Study of Scintillation Beta Microprobes

C.L. Woody, S.P. Stoll, D.J. Schlyer, M. Gerasimov, P. Vaska, S. Shokouhi,
N. Volkow, J.S. Fowler, S.L. Dewey

Brookhaven National Laboratory
Upton, New York

Abstract—Several types of scintillation microprobes have recently been developed to directly measure positron activity from radiotracers in live animals. These probes consist of either a small LSO crystal or plastic scintillator coupled to an optical fiber that is read out with a photomultiplier tube operated in a single photon counting mode. In this study, a comparison is made between the two types of probes in terms of their sensitivity to both positrons and gammas. It was found that LSO offers very high sensitivity to positrons due to its high density and light output, and allows the construction of very small probes for certain applications. The LSO probe can also provide effective discrimination between positrons and gammas, and provide better localization of positron decays, using pulse height discrimination. Results are also given on the use of the microprobe on live laboratory animals.

I. INTRODUCTION

A great deal of effort is currently under way using PET imaging in small animals. This includes the development of radiotracers, which are ultimately used in humans, that require the study of the neurophysiological activity in laboratory animals. These studies are currently limited by the spatial resolution of the PET scanner, and that they must be conducted with anesthetized animals, which severely depresses brain functions. As a result, there has been considerable interest in an alternative approach that uses a small, intracerebral microprobe that can directly measure positron decays in living tissue [1,2]. These probes can be used to study the activity of radiotracers in a highly localized region of the brain that cannot be visualized with current scanners, and can be used in conjunction with microdialysis in the study of chemical kinetics inside the brain. In addition, these probes can also be used to measure the radiotracer activity in the blood.

This paper investigates the properties of two different types of scintillation microprobes, one made of a dense, inorganic crystal (LSO), and another made of plastic scintillator. A comparison has been made of the detection sensitivities of these two types of probes for positrons and gamma rays, and their ability to localize positron decays using pulse height discrimination. Results are also given on the performance of these probes using live laboratory animals.

II. COMPARISON OF MATERIALS

To detect positrons from radiotracers labeled with isotopes such as ^{11}C and ^{18}F , the material used should have a high sensitivity to positrons in the 0.1-1.0 MeV energy range. Lutetium oxyorthosilicate (LSO) is a new scintillating material that readily meets these requirements. Figure 1 shows the range and energy loss for positrons in LSO compared with polystyrene plastic scintillator [3]. It shows that in this energy range, the energy loss in LSO is on the order of 1 MeV/mm, and that positrons can be effectively stopped with a probe having dimensions on the order of a few hundred microns. As an example, the average positron energy for ^{11}C is 386 keV, and the maximum energy is 960 keV. This corresponds in LSO to an average range of 0.3 mm and a maximum range of 0.9 mm. Given that LSO also has a very high light output ($\sim 25,000$ photons per MeV), an energy deposit of a few tenths of an MeV produces an easily detectable signal for counting positron decays.

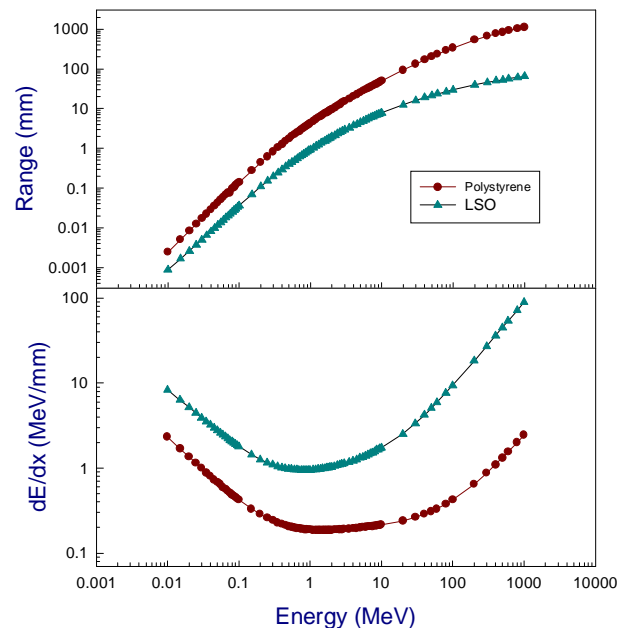


Fig. 1. Range and energy loss for positrons in LSO and polystyrene plastic scintillator.

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By comparison, the average range for positrons from ^{11}C in plastic scintillator is 1.3 mm, and the maximum range is 4.0 mm. The energy loss is approximately five times less than in LSO (~ 0.2 MeV/mm), and the light output is also considerably lower ($\sim 10,000$ photons per MeV). Therefore, for the same size probe, the detectable signal produced by a plastic scintillator probe will be considerably smaller than for an LSO probe. However, due to the shorter attenuation length for gamma rays in LSO compared to plastic (1.16 cm vs 10.4 cm), the LSO probe will have a higher sensitivity to background gamma rays produced by positron annihilation in the surrounding tissue.

Due to its shorter range for positrons and higher light output, LSO probes can be made considerably smaller than plastic probes and still have good sensitivity. This can lead to other applications, such as the ability to measure radiotracer activity in blood flow, or to better localize the positron activity in the brain, as described below.

III. PROBE CONSTRUCTION

A series of tests were carried out to determine the optimum size of the crystal for the LSO probes consistent with obtaining the maximum possible light output. The crystals tested were cylindrical in shape with diameters ranging from 0.3-0.5 mm, and lengths from 0.5 to 5.0 mm. The crystals were produced using a micromachining technique and were polished to some degree on all sides [4]. They were carefully mounted into a custom designed gluing fixture and coupled to quartz fibers using a UV curable epoxy. The fibers were silica core/silica clad material manufactured by 3M, and had diameters ranging from $600\text{ }\mu\text{m}$ (FT-600-UMT, numerical aperture 0.39) used for the 0.5 mm diameter crystals, to $365\text{ }\mu\text{m}$ (FG-365-UER, numerical aperture 0.22) for the 0.3 mm crystals.

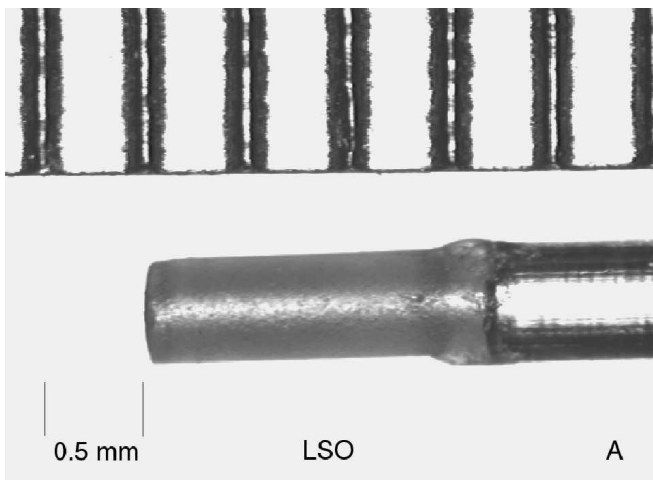


Fig. 2. 0.5 mm dia. x 1.5 mm long LSO crystal glued to $600\text{ }\mu\text{m}$ diameter quartz fiber.

Figure 2 shows a 0.5 mm diameter x 1.5 mm long bare crystal coupled to the fiber. The crystal was subsequently wrapped with several layers of thin ($\sim 0.0015''$) white reflecting teflon in order to improve the light collection efficiency. In addition, a single layer of polyester shrink tubing, with a wall thickness of $.0007''$, was placed over the wrapped crystal in order to encapsulate the probe tip and protect it from coming in contact with blood or tissue. Figure 3 shows a completed probe tip with the teflon wrapping and shrink tubing.

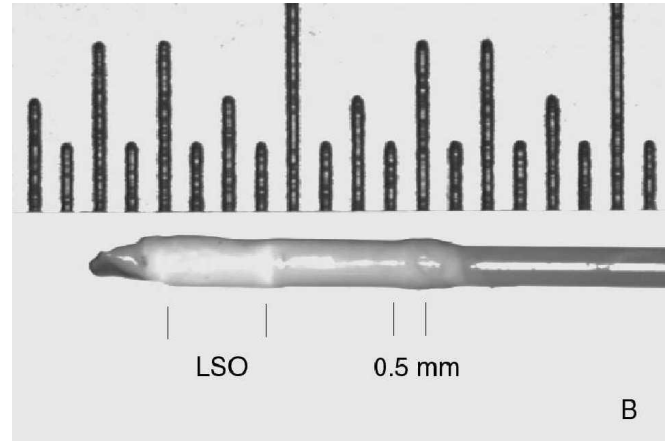


Fig. 3. Completed probe tip with teflon wrapping and polyester shrink tubing at the end of the fiber.

Smaller LSO probes were constructed in a similar manner. Figure 4 shows a 0.3 mm diameter x 0.5 mm long LSO probe mounted inside an 18 gauge syringe needle. This probe is sufficiently small that it can be inserted into a vein or artery and used to measure radiotracer activity in the blood. The use of the probe in this application is discussed in Section V.

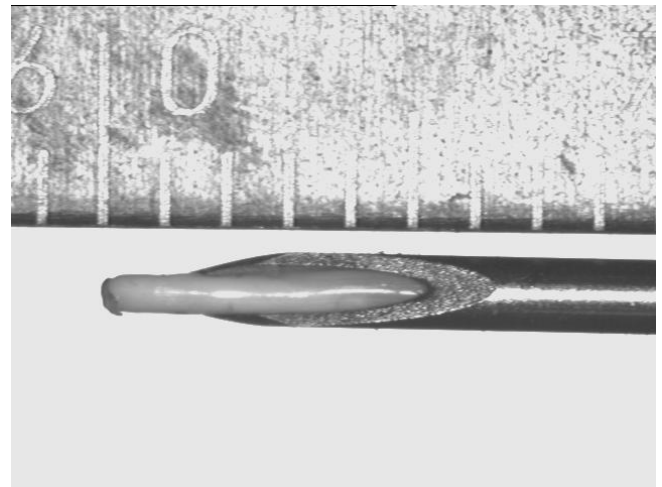


Fig. 4. LSO scintillation microprobe 0.3 mm dia. x 0.5 mm long shown with teflon wrapping and polyester shrink tubing inside an 18 gauge syringe needle.

Plastic scintillation probes were constructed similar to those described in [1]. They consisted of a 1.0 mm diameter x 1.0 mm long piece of BCF-12 plastic scintillator coupled to a clear plastic fiber. The probes were wrapped with several layers of teflon reflector and one layer of polyester shrink tubing in a manner similar to the LSO probes.

IV. LIGHT OUTPUT AND SENSITIVITY MEASUREMENTS

The light produced by the crystal or plastic scintillator was measured with a low noise phototube (Hamamatsu R647P) that was capable of detecting single photons, and the signals were read out and digitized using a LeCroy 2249 ADC. The phototube was calibrated in terms of the number of ADC channels per photoelectron and used to determine the photoelectron yield for each scintillator. For counting positrons or gamma rays, the phototube signal was integrated using an ORETC 474 shaping amplifier with an integration time of 200 ns, and then discriminated and counted with a scaler

Figure 5 shows the photoelectron yield for the LSO probe and the plastic probe exposed to pure betas (negative electrons) from a ^{32}P source, compared with gammas from a ^{137}Cs source. The ^{32}P beta has an average energy of 0.695 MeV, similar to the 0.662 MeV gamma ray from ^{137}Cs , and an endpoint energy of approximately 1.7 MeV. It is clear that the LSO probe gives a much larger signal (over 300 photoelectrons for the endpoint of the beta decay spectrum), and allows a clear separation of betas and gammas. The signal from the plastic probe is much lower (<50 photoelectrons), and there is essentially no discrimination between betas and gammas.

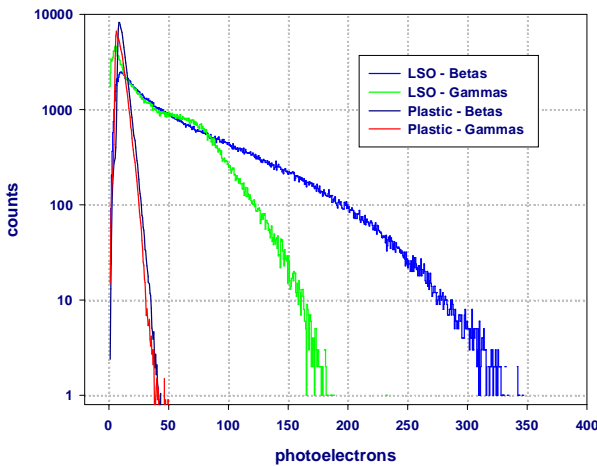


Fig. 5. Pulse height measured in terms of photoelectrons detected by the phototube for pure betas (^{32}P) and gammas (^{137}Cs) for the LSO and plastic scintillation probes.

The overall sensitivity of each probe to betas and gammas depends on the size of the probe, the amount of energy deposited in the probe material, and the efficiency for detecting the scintillation light that is produced. The sensitivity S ($\text{Hz}/\mu\text{Ci/cc}$) can be expressed as:

$$S = F \cdot \int_V dV \cdot \left[I \cdot \frac{dE}{dx} \cdot Y \cdot \varepsilon(N_{pe}) \right] \quad (1)$$

where F is the flux in particles/ cm^2/s hitting the probe normalized to the isotope concentration in $\mu\text{Ci/cc}$, I is the interaction probability for a given particle type (effectively equal to one for positrons, and determined by the attenuation length of the scintillator for gammas), dE/dx is the energy deposit per unit length, Y is the signal produced in terms of photoelectrons per MeV, and $\varepsilon(N_{pe})$ is the detection efficiency. The detection efficiency is a function of the number of photoelectrons produced and the threshold set in the electronics for detecting the signal. By varying the threshold, one can therefore change the relative sensitivity of the probe to positrons and gammas. If we identify the terms in brackets as the response of the volume element dV to the flux F , then the sensitivity of the probe is obtained by integrating this response over the volume V of the detector.

TABLE I
SENSITIVITIES FOR LSO AND PLASTIC SCINTILLATOR PROBES

Material	LSO	LSO	Plastic
Size	0.3 x 0.5 mm	0.5 x 1.5 mm	1.0 x 1.0 mm
Volume	0.035 mm ³	0.295 mm ³	0.785 mm ³
Sensitivity (Hz/ $\mu\text{Ci/cc}$)	10.1	20.7	51.2

The sensitivities of the LSO and plastic probes were measured using an aqueous solution containing ^{11}C with a known concentration of 63.4 $\mu\text{Ci/cc}$. In each case, the detection threshold was set to the lowest possible value, which was slightly greater than one photoelectron. The measured sensitivities are given in Table I. The sensitivities of the small and large LSO probes were 10.1 $\text{Hz}/\mu\text{Ci/cc}$ and 20.7 $\text{Hz}/\mu\text{Ci/cc}$ respectively, while the sensitivity of the plastic probe was 51.2 $\text{Hz}/\mu\text{Ci/cc}$. The ratio of the sensitivities of the large LSO probe to the plastic probe scales roughly as the ratio of their volumes, as one would expect from (1) if the response of the two probes was similar. However, for the LSO probes, the sensitivity of the smaller probe dropped to only half that of the larger probe, while the volume decreased by more than a factor of 8. This result is somewhat surprising, but could be due to the fact that the response of the smaller probe was higher. It was found that the number of photoelectrons produced by the smaller probe for a given energy deposit was higher than in the larger probe, which was most likely due to better light collection with the smaller geometry.

While for the plastic probe it is necessary to set the detection threshold as low as possible in order to be efficient for betas, for the LSO probe, it is possible to raise the detection threshold and vary the sensitivity to both betas and gammas. Figure 6 shows the spectrum for ^{32}P betas for various levels of discrimination for an LSO probe. At a threshold of ~ 600 mV, virtually all of the gamma ray background can be eliminated, with a corresponding loss of sensitivity of about a factor of seven. With LSO, this still provides enough sensitivity for most applications. However, depending on its particular use and the environment surrounding the probe, a lower threshold could also be used with only a modest increase in sensitivity to gamma rays.

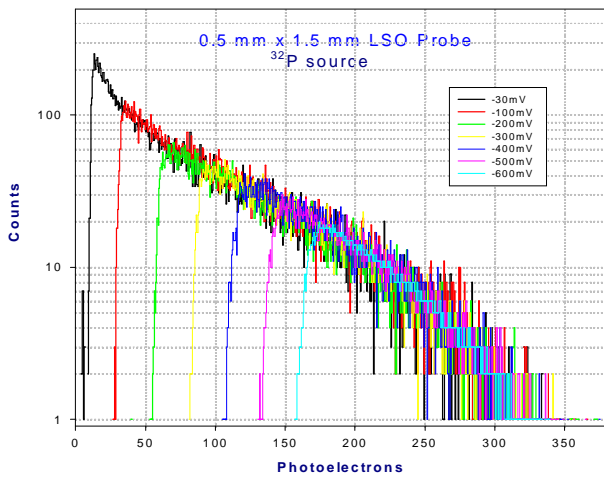


Fig. 6. Pulse height spectra in LSO for various thresholds

We have used an optical simulation program [5] to try and estimate the gamma ray background for an LSO probe in the environment of a distributed source of positrons and gamma rays. The program was used to determine the number of particles (betas and gammas) impinging on the probe from a surrounding volumetric source. The dimensions of the probe were taken to be 0.5 mm diameter by 1.5 mm long, surrounded by a cylindrical source of varying radius, and extending one radius above and below the probe. The effective flux was given by the total activity in the source volume multiplied by the geometrical efficiency for a decay particle to hit the probe. This flux was found to increase linearly with source radius. No correction was made for attenuation, although for distances greater than 10 cm (the attenuation length for 511 keV gamma rays in tissue), this correction becomes important.

If one assumes an effective radius of 10 cm for gammas, and a maximum radius of 4 mm for detecting positrons (corresponding to the maximum range for positrons from ^{11}C in tissue), the ratio of gammas to positrons hitting the probe is 21.6. The probability for a gamma to interact in the probe

is determined by the photon attenuation length in LSO of 1.16 cm. Assuming an effective thickness of ~ 1 mm for the probe, this gives an average interaction probability of 0.082, and results in an effective ratio of gammas converting in the probe to positrons of 1.8. The threshold cut described above can then be applied to reduce the rate of observed gammas by an additional factor depending on the threshold.

While raising the detection threshold for the LSO probe reduces its sensitivity to gamma rays, it can also be used to improve the spatial resolution. The spatial resolution is determined mainly by the range of the positrons in the tissue surrounding the probe, which is typically on the order of a few millimeters. However, by selecting the upper most part of the beta spectrum, one can select only the most energetic positrons that were produced in a region very close to the probe. All other positrons will lose energy as they pass through the tissue from farther away and will deposit a lower energy in the crystal. Therefore, by the use of pulse height discrimination, one can limit the region of sensitivity around the probe in order to achieve better spatial resolution.

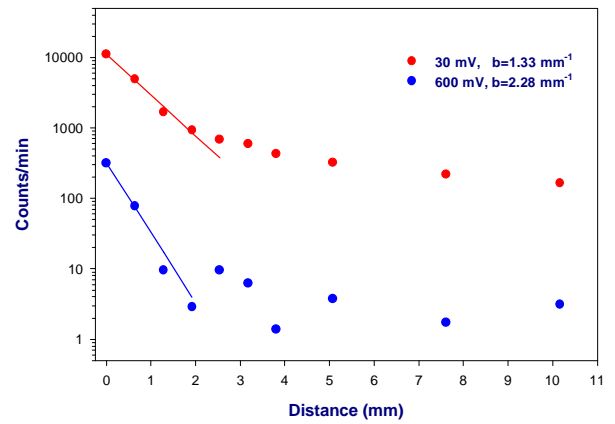


Fig. 7. Sensitivity of the LSO probe to positrons as a function of distance in water for two different thresholds (Note: count rates between the two threshold curves are not normalized).

This effect was studied by measuring the sensitivity of the probe to a point positron source as a function of distance from the probe for various detection thresholds. The point source consisted of the activated tip of a vanadium wire which was immersed in a container of water (used to simulate tissue or blood) along with an LSO probe. The resulting data at the highest and lowest thresholds are shown in Fig. 7. The spectrum clearly becomes steeper at the higher threshold due to the fact that only the highest energy betas produced close to the probe have sufficient energy to be detected. An exponential fit (e^{-bx}) to the spectrum close to the probe shows that the slope parameter b changes from 1.33 mm^{-1} at the lowest threshold to 2.28 mm^{-1} at the highest threshold. This corresponds to a decrease in the size of the effective detection region (characterized by the FWHM of the distance distribution) from ~ 1.0 mm to ~ 0.6 mm.

V. RESULTS FROM ANIMAL STUDIES

A series of tests were carried out using the LSO probes with live laboratory animals. The first was conducted on a rat to determine if the probe could detect the presence of the drug methylphenidate labeled with ^{11}C . This drug is expected to be taken up in the nucleus accumbens region of the brain, and to reside there for up to several hours after being introduced into the body.



Fig. 8. LSO microprobe prepared for implantation into the brain of a rat for drug uptake study.

Figure 8 shows a 0.5 mm diameter x 1.5 mm long LSO probe prepared for implantation into the brain of a rat. The probe was implanted using standard surgical techniques used for microdialysis probes. For this initial test, the rat was anesthetized, but this technique permits these studies to be carried out on an awake animal, as is routinely done in microdialysis, thus allowing much greater flexibility for radiotracer studies.

The drug was administered via an intra-peritoneal (IP) injection and contained approximately 0.4 mCi of ^{11}C activity at the time of injection. Data from the probe was collected with the threshold set to its minimum value (30 mV) such that the probe would be sensitive to all events (gammas plus positrons). This provided a measure of the count rate for the gamma ray background as well as for positrons. The count rate due to random background was measured before injection and found to be negligible (<0.1 Hz). Recording of the probe data started within 1.7 minutes after injection of the drug.

Figure 9a shows the raw measured count rate as a function of time, and Figure 9b shows the count rate corrected for the ^{11}C decay time. The initial increase observed is due to gamma rays, since with the IP injection, the drug had not yet had time to reach the brain. The count rate then increased steadily until reaching a plateau of approximately 60 Hz after 20 minutes, corresponding to roughly three times the

level of the gamma ray background. This level of activity remained constant for several hours, which is precisely the behavior one would expect for the uptake of methylphenidate in the nucleus accumbens region of the brain.

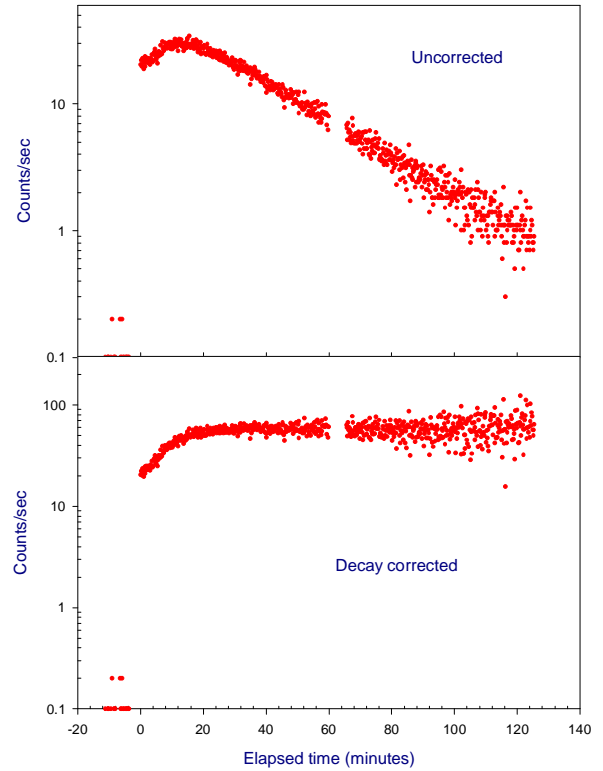


Fig. 9. Count rate measured with an LSO probe for the uptake of [^{11}C]-methylphenidate in the nucleus accumbens region of the brain of a rat. a) uncorrected raw data b) data corrected for ^{11}C decay time.

A second test was carried out to measure the radiotracer activity in the blood of a baboon that was undergoing a PET scan. Normally, the arterial input function for this type of study is obtained by taking blood samples at approximately 2.5 second intervals using an automated blood sampling apparatus [6], and then determining the activity in these samples in an external well counter. For this study, a small 0.3 mm diameter x 0.5 mm long LSO probe (similar to the one shown in Fig. 4) was inserted into the blood flow as it was being withdrawn, and the count rate was measured continuously as a function of time. The drug injected was tyrosine labeled with 2.89 mCi of ^{11}C .

The results on the measurement of the input function using the probe compared with the data obtained from the well counter are shown in Figure 10. The data show excellent agreement in the longer decay part of the spectrum, but the microprobe was able to provide a more continuous measure of the input function starting at the time of injection, and can therefore provide a better determination of the peak. In addition, the probe technique also does not

require having to withdraw blood samples, which offers greater potential for its use in studies involving rats or other small animals whose blood volume is too small to permit external sampling.

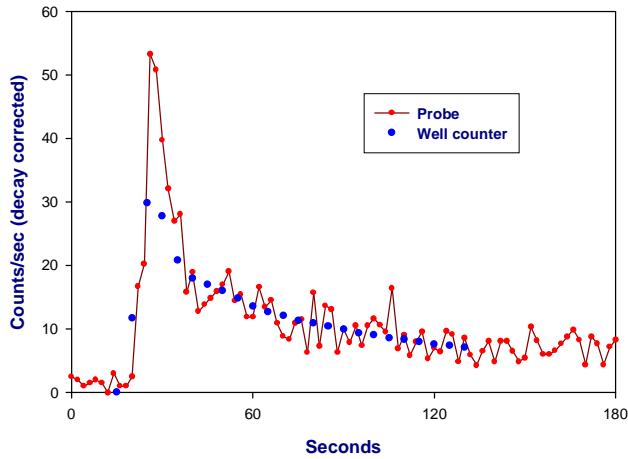


Fig. 10. Activity of $[^{11}\text{C}]$ -tyrosine measured in the blood flow as it was being withdrawn from a baboon during a PET scan using a syringe mounted LSO microprobe compared with the activity measured in an external well counter. Data are relatively normalized.

VI. SUMMARY AND CONCLUSIONS

A comparison has been made of LSO and plastic scintillation microprobes and their use for measuring positron labeled radiotracers in the blood and tissue of small animals. Both types of probes show good sensitivity to positrons, and can be used effectively as intracerebral devices to directly measure the positron activity in the animal brain. However, the LSO probe has a much higher light output than the plastic probe, which offers the potential to use pulse height discrimination to distinguish between betas and gammas and to improve the spatial resolution. The high sensitivity of LSO also permits the construction of much smaller probes, allowing their use in other applications, such as measuring the arterial input function in blood flow. These results are very encouraging for the use of scintillation microprobes in the future development of radiotracers using live, awake animals.

VII. REFERENCES

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